1652

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Group Art Unit 1652

Re: U.S. Utility Patent Application
Appl. No.: 09/558,421; Filed: April 26, 2000
For: **Mutant DNA Polymerases and Uses Thereof**
Inventor: Deb K. CHATTERJEE
Our Ref: 0942.3600003/RWE/BJD

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Supplemental Suggestion by Applicant for Interference Under 37 C.F.R. § 41.202(a); and

2. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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RWE/BJD/AWL:ddc
Enclosures

317571_1.DOC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 9752
Deb K. CHATTERJEE	Art Unit: 1652
Appl. No.: 09/558,421	Examiner: Rao, Manjunath N.
Filed: April 26, 2000	Atty Docket: 0942.3600003/RWE/BJD
For: **Mutant DNA Polymerases and Uses Thereof**	

Supplemental Suggestion by Applicant for Interference Under 37 C.F.R. § 41.202(a)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Further to Applicant's Request for Interference filed pursuant to the provisions of 37 C.F.R. § 1.607 and 1.643 on December 4, 2001, which is herein incorporated by reference, and as requested by Examiner Rao during a telephone conference on September 9, 2004, Invitrogen Corporation, assignee of record of the entire interest of the present application,[1] provides herein a supplemental suggestion for the declaration of an interference between the present application (U.S. Appl. No. 09/558,421; hereinafter "the '421 application") and U.S. Patent No. 5,614,365 (hereinafter "the '365 patent"), to Tabor *et al.*, assigned to President & Fellow [sic; Fellows] of Harvard College, Cambridge, Massachusetts. The '365 patent is of record in the present case as Doc. No. A1 listed on the Form PTO-892 attached to Paper No. 4.

[1]The present application was assigned by Deb K. Chatterjee to Life Technologies, Inc., in an Assignment recorded on December 21, 1995, at Reel 7842, Frame 0273. Life Technologies, Inc. merged with Invitrogen Corporation on September 12, 2000, with Invitrogen Corporation being the surviving entity. A copy of the merger document, evidencing this merger, was recorded with the Assignment Branch of the USPTO on December 4, 2001, beginning at Reel 012339, Frame 0912. Therefore, Invitrogen Corporation is the assignee of record of the entire interest of the present application.

As noted in the cross-reference section of its specification, the '421 application is a continuation of U.S. Application No. 08/576,759, filed December 21, 1995, which is a continuation of U.S. Application No. 08/537,397, filed October 2, 1995, which is a continuation-in-part of U.S. Application No. 08/525,057, filed September 8, 1995. The '365 patent issued from U.S. Application No. 08/337,615, filed November 10, 1994, which is a continuation-in-part of U.S. Application No. 08/324,437, filed October 17, 1994.

Both the '365 patent and the present application disclose and claim mutant DNA polymerases, and DNA encoding them, comprising a Tyr →Phe mutation at a position corresponding to Phe_{570} of wild-type T5 polymerase. Applicant specifically refers to the remarks contained in the Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on December 4, 2001, and in the Supplemental Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on February 2, 2002, which are reiterated and incorporated herein by reference, to establish conception and reduction to practice of his invention prior to the earliest available filing date of the '365 patent. Since the '365 patent and the '421 application contain at least one claim directed to the same patentable invention, as discussed below, Applicant respectfully suggests that an interference be expeditiously declared between the '421 application and the '365 patent.

I. Identification of Patent

In accordance with 37 C.F.R. § 41.202(a)(1), the patent with which Applicant suggests that an interference be declared is U.S. Patent No. 5,614,365, which issued on March 25, 1997, to Tabor *et al.*, and which is assigned to President & Fellow [sic; Fellows] of Harvard College, Cambridge, Massachusetts.

II. Proposed Count and Identification of Claims Corresponding to the Proposed Count

A. Proposed Count

In accordance with 37 C.F.R. § 41.202(a)(2), the following count is proposed:

> A DNA molecule comprising a coding sequence for a mutant protein, wherein said mutant protein is a mutant DNA polymerase selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase, and wherein said mutant DNA polymerase comprises a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase.

This proposed count, which relates to a DNA molecule encoding a mutant DNA polymerase, encompasses all patentable claims which correspond to the count.

B. Identification of Claims Corresponding to the Proposed Count

In accordance with 37 C.F.R. § 41.202(a)(2), Applicant hereby identifies claims 1-3, 5-11, 32, 40, 55, 56, 63, 69 and 70 in the '365 patent as being directed to the same patentable invention as the proposed count, and which should therefore be designated as corresponding to the proposed count.

1. Claim 1

Claim 1 of the '365 patent recites:

> 1. Modified gene encoding a modified Pol I-type DNA polymerase wherein said modified gene is modified to encode a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site to

> increase ability of said modified DNA polymerase to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to the ability of a corresponding naturally-occurring unmodified DNA polymerase by at least 20-fold.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 1 and 15, since it encompasses modified DNA polymerases of the Pol I family with specific mutations corresponding to those recited in the count. While claim 1 of the '365 patent refers to Pol I type DNA polymerases and Applicant's claim 1 recites a Markush group of specific polymerases, there is overlap between the two groups of polymerases. The Pol I family of polymerases is described in the '365 patent at col. 7, lines 40-46. This family of polymerases includes *Streptococcus pneumoniae* polymerase I, *Thermus aquaticus* polymerase I, *Thermus flavus* DNA polymerase, T5 DNA polymerase, and bacteriophage Spo 1 DNA polymerase, as well as other polymerases. Each of these specifically enumerated polymerases is recited in the Markush group in Applicant's claim 1 and in the proposed count. In addition, *Thermus aquaticus* polymerase is specifically recited in Applicant's claim 15 and in the proposed count. Finally, "a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase" recited in the count and in Applicant's claim 1, and substitution of tyrosine for phenylalanine at position 667 in Taq polymerase as recited in Applicant's claim 15, corresponds to a tyrosine substitution at position 762 of *E. coli* Pol I (*see* specification of '421 application, at page 8, lines 18 and 25), and to a tyrosine substitution at position 526 of T7 DNA polymerase (*see* '365 patent at Figs. 3 and 4, and at col. 3, line 59, to col. 4, line 4). Therefore, claim 1 of the '365 patent should be designated as corresponding to the count.

2. Claim 2

Claim 2 of the '365 patent is directed to:

> 2. The modified gene of claim 1 wherein said modified DNA polymerase has sufficient DNA polymerase activity for use in DNA sequencing when combined with any factor necessary for said DNA polymerase activity.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 have the characteristic of having sufficient DNA polymerase activity for use in DNA sequencing when combined with any factor necessary for said DNA polymerase activity. While this characteristic is not expressly recited in Applicant's claim 1 or in the proposed count, "[t]he mutant-DNA polymerases of this invention may also be used for DNA sequencing, DNA labeling, and amplification reactions." Specification of '421 application, at page 17, lines 20-21. Thus, the specification of the '421 application provides that at least a subset of the mutant DNA polymerases disclosed and claimed therein, and encompassed by Applicant's claim 1, are intended for use in DNA sequencing, and therefore must possess "sufficient DNA polymerase activity for use in DNA sequencing when combined with any factor necessary for said DNA polymerase activity." As such, claim 2 of the '365 patent should be designated as corresponding to the count.

3. Claim 3

Claim 3 of the '365 patent is directed to:

> 3. The modified gene of claim 1 wherein said modified DNA polymerase

> has less than 500 Units exonuclease activity per mg polymerase.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 have less than 500 Units exonuclease activity per mg polymerase. While this characteristic is not expressly stated in Applicant's claim 1 or in the proposed count, the specification of the '421 application provides that:

> The present invention is further directed to a mutant DNA polymerase produced by the methods of the present invention, having substantially reduced exonuclease activity. . . . Preferably, the exonuclease activity is less than about 1 unit/mg protein. More preferably, the exonuclease activity is less than about 0.1 units/mg protein. Even more preferably, the exonuclease activity is less than about 0.003 units/mg protein. Most preferably, the exonuclease activity is less than about 0.0001 units/mg protein.

Specification of '421 application, at page 16, lines 5-13. Thus, the specification of the '421 application provides that at least a subset of the mutant-DNA polymerases disclosed and claimed therein, and encompassed by Applicant's claim 1, have less than 500 Units exonuclease activity per mg polymerase. Hence, claim 3 of the '365 patent should be designated as corresponding to the count.

4. Claim 5

Claim 5 of the '365 patent is directed to:

> 5. The modified gene of claim 1 wherein said modified DNA polymerase is a thermostable enzyme.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of

the count and Applicant's claim 1 are thermostable enzymes (*e.g.*, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase and *Thermatoga maritima* polymerase). Hence, claim 5 of the '365 patent should be designated as corresponding to the count.

5. Claim 6

Claim 6 of the '365 patent is directed to:

> 6. The modified gene of claim 5 wherein said thermostable enzyme is selected from the group consisting of DNA polymerase encoded by *Thermus aquaticus*, *Thermus thermophilus*, *Thermus flavus*, and *Bacillus sterothermophilus*.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 are also recited in claim 6 of the '365 patent (*i.e.*, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase and *Thermus thermophilus* polymerase). Hence, claim 6 of the '365 patent should be designated as corresponding to the count.

6. Claim 7

Claim 7 of the '365 patent is directed to:

> 7. The modified gene of claim 1 wherein said ability of said polymerase to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide is increased at least 25-fold compared to the corresponding naturally-occurring unmodified DNA polymerase.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of

the count and Applicant's claim 1 have the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide increased by at least 25-fold compared to the corresponding naturally-occurring unmodified DNA polymerase. The '365 patent defines the "increased ability" referred to in claims 7-11, as a situation in which:

> [t]he DNA polymerase is able to better incorporate a dideoxynucleotide. That is, it discriminates to a lesser extent than a corresponding naturally-occurring DNA polymerase against a dideoxynucleotide compared to a deoxynucleotide. . . . The term "increased" means to provide a measurable difference in ability to incorporated such dideoxynucleotides.

The '365 patent, column 6, lines 54-58. The '365 patent discloses also that an exemplary enzyme:

> is *E. coli* DNA polymerase I which (as noted herein) discriminates approximately 140-1,100 fold against incorporation of dideoxynucleotides compared to deoxynucleotides. By the method of this invention an enzyme can be derived (by alteration of only one or two amino acids) that actually prefers ddNTPs over dNTPS--that is, the ability of the polymerase to incorporate dideoxynucleotides has been increased by an average of 1,000 fold.

The '365 patent, column 6, line 66 to column 7, line 7. Thus, by the definition provided in the '365 patent, the production of a non-discriminatory mutant *E. coli* DNA polymerase I is equivalent to producing a DNA polymerase with an increase of at least 1000-fold in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase. While this characteristic is not expressly recited in Applicant's claim 1 or in the proposed count, the specification of the '421 application provides that "T5, Taq, Tne, Tma and other DNA polymerases can be made nondiscriminatory towards

dideoxynucleotide and perhaps other nonnatural nucleotides by simple modification of a specific phenylalanine residue to a tyrosine residue." Specification of '421 application, at page 27, lines 10-15. Thus, at least a subset of the nondiscriminatory DNA polymerases described and claimed in the '421 application, when defined as in the '365 patent, are at least 25-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase. Hence, claim 7 of the '365 patent should be designated as corresponding to the count.

7. Claim 8

Claim 8 of the '365 patent is directed to:

> 8. The modified gene of claim 1 wherein said ability is increased at least 50-fold.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 are at least 50-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase. For at least the same reasons as set forth for claim 7, which are incorporated and reiterated herein, claim 8 of the '365 patent should be designated as corresponding to the count.

8. Claim 9

Claim 9 of the '365 patent is directed to:

> 9. The modified gene of claim 1 wherein said ability is increased at least 100-fold.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 are at least 100-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally-occurring unmodified DNA polymerase. For at least the same reasons as set forth for claim 7, which are incorporated and reiterated herein, claim 9 of the '365 patent should be designated as corresponding to the count.

9. Claim 10

Claim 10 of the '365 patent is directed to:

> 10. The modified gene of claim 1 wherein said ability is increased at least 500-fold.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claim 1, since a number of the enzymes recited in the Markush group of the count and Applicant's claim 1 are at least 500-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase. For at least the same reasons as set forth for claim 7, which are incorporated and reiterated herein, claim 10 of the '365 patent should be designated as corresponding to the count.

10. Claim 11

Claim 11 of the '365 patent recites:

> 11. Method for production of a modified Pol I-type DNA polymerase having an increased ability to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to ability of a corresponding naturally-occurring unmodified DNA polymerase

> comprising steps of: providing a nucleic acid molecule encoding a DNA polymerase and mutagenizing said nucleic acid molecule to incorporate one or more base changes in nucleotide base sequence at a region that encodes its dNMP binding site to encode a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in the dNMP binding site to alter ability of said polymerase encoded by said nucleic acid to incorporate a dideoxynucleotide by at least 20-fold.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 6 and 20, for essentially the same reasons outlined above with respect to claim 1 of the '365 patent, which are reiterated and incorporated herein. Hence, claim 11 of the '365 patent should be designated as corresponding to the count.

11. Claim 32

Claim 32 of the '365 patent recites:

> 32. Recombinant nucleic acid encoding any of the DNA polymerases of claims 27 to 31.

Claims 27 and 28, from which claim 32 depends in part, recite:

> 27. A *Thermus aquaticus* DNA polymerase having a tyrosine at residue 667.
>
> 28. An *E. coli* DNA polymerase I having a tyrosine at residue 762.

Hence, claim 32 of the '365 patent encompasses a recombinant nucleic acid molecule encoding (a) a Taq DNA polymerase having a tyrosine residue substituted in place of the phenylalanine residue at position 667 in the wild-type Taq sequence; and (b)

an *E. coli* Pol I DNA polymerase having a tyrosine residue substituted in place of the phenylalanine residue at position 762 in the wild-type *E. coli* Pol I sequence. This claim therefore is directed to the same patentable invention as Applicant's claim 1 and the proposed count, since "a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase" as recited in the proposed count would correspond to a substitution of tyrosine for phenylalanine at residue 667 of Taq, and at position 762 of *E. coli* Pol I. *See* specification of '421 application at page 8, lines 18, 20 and 25.

Claim 29, from which claim 32 of the '365 patent also depends, recites:

> 29. Purified Pol I type DNA polymerase having a tyrosine residue at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site provided that said polymerase is not a T7-type DNA polymerase or a mitochondrial DNA polymerase.

By its dependence from claim 29, claim 32 of the '365 patent therefore is similar to claim 1 of the present application and to claim 1 of the '365 patent. This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 1 and 15, for essentially the same reasons outlined above with respect to claim 1 of the '365 patent which are reiterated and incorporated herein. For at least this additional reason, then, claim 32 of the '365 patent should be designated as corresponding to the count.

12. Claim 40

Claim 40 of the '365 patent is directed to:

> 40. Recombinant Nucleic acid encoding the polymerase of any of claims 33-39.

Claim 36, from which claim 40 depends in part, recites:

> 36. Recombinant Thermophilic DNA polymerase that discriminates against a ddNMP relative to a corresponding deoxynucleotide by less than a factor of 100 and wherein said DNA polymerase includes a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

By its dependence from claim 36, claim 40 of the '365 patent encompasses a recombinant nucleic acid molecule encoding (a) a recombinant thermophilic DNA polymerase; (b) that discriminates against a ddNMP relative to a corresponding deoxynucleotide by less than a factor of 100; and that (c) includes a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site. This claim is therefore directed to the same patentable invention as recited in Applicant's claim 1 and the proposed count, for essentially the same reasons outlined above with respect to claims 1, 7, and 32 of the '365 patent, which are reiterated and incorporated herein. For at least these reasons, then, claim 40 of the '365 patent should be designated as corresponding to the count.

13. Claim 55

Claim 55 of the '365 patent is directed to:

> 55. Purified nucleic acid encoding a DNA polymerase according to claim 47.

Claim 47 of the '365 patent is directed to:

> 47. The purified thermostable DNA polymerase according to any of claim 46 [sic] wherein said DNA polymerase is not a naturally-occurring DNA polymerase.

Claim 46 of the '365 patent is directed to:

> 46. A purified thermostable DNA polymerase having a deoxynucleotide binding site with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q wherein each N_1-N_3 and N_5-N_7 is independently any amino acid and N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

By its direct dependence from claim 47 (and thereby its indirect dependence from claim 46), claim 55 of the '365 patent encompasses a purified nucleic acid encoding a non-naturally occurring thermostable DNA polymerase having a deoxynucleotide binding site with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q wherein each N_1-N_3 and N_5-N_7 is independently any amino acid and N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site. While the limitation of claim 46 is not expressly recited in Applicant's claim 1 or in the proposed count, Example 1 of the '421 application teaches the site-directed mutagenesis of a DNA molecule encoding T5 DNA polymerase to encode a mutant T5 DNA

polymerase having an O-helix domain with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q where N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526, and where each N_1-N_3 and N_5-N_7 is independently any amino acid. Specification of '421 application, page 21, line 6 to page 23, line 30. Because the claim of the proposed count and claim 1 of the '421 application encompass DNA molecules comprising a coding sequence for the mutant DNA polymerase of example 1 of the '421 application, claim 55 of the '365 patent is therefore directed to the same patentable invention as the proposed count and claim 1 of the '421 application. Hence, claim 55 of the '365 patent should be designated as corresponding to the count.

14. Claim 56

Claim 56 of the '365 patent is directed to:

> 56. Purified nucleic acid encoding a DNA polymerase according to claim 49.

Claim 49 of the '365 patent is directed to:

> 49. The purified DNA polymerase according to claim 47 wherein said polymerase is modified from a *Thermus aquaticus* DNA polymerase to have a tyrosine residue at a position corresponding to residue 667 of a corresponding naturally occurring unmodified polymerase

Claim 47 of the '365 patent is directed to:

> 47. The purified thermostable DNA polymerase according to any of claim 46 [sic] wherein said DNA polymerase is not a naturally-occurring DNA polymerase.

Claim 46 of the '365 patent is directed to:

> 46. A purified thermostable DNA polymerase having a deoxynucleotide binding site with the sequence K N_1 N_2 N_3

> N_4 N_5 N_6 N_7 Y G/Q wherein each N_1-N_3 and N_5-N_7 is independently any amino acid and N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

By its direct dependence from claim 49 (and thereby its indirect dependence from claims 46 and 47), claim 56 of the '365 patent encompasses a purified nucleic acid encoding a thermostable, non-naturally occurring modified *Thermus aquaticus* DNA polymerase having a deoxynucleotide binding site with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q with N_4 being a tyrosine residue at an amino acid position corresponding to 667 the naturally occurring unmodified polymerase. While the limitation of claim 46 is not expressly recited in Applicant's claim 1 or in the proposed count, Example 1 of the '421 application teaches the site-directed mutagenesis of a DNA molecule encoding T5 DNA polymerase to encode a mutant T5 DNA polymerase having an O-helix domain with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q where N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526, and where each N_1-N_3 and N_5-N_7 is independently any amino acid. Specification of '421 application, page 21, line 6 to page 23, line 30. Because the claim of the proposed count and claims 1 and 15 of the '421 application encompass DNA molecules comprising a coding sequence for the mutant DNA polymerase of example 1 of the '421 application, claim 56 of the '365 patent is therefore directed to the same patentable invention as the proposed count and claim 1 of the '421 application. This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 1 and 15, for essentially the same reasons outlined above with respect to claims 1 and 55 of the '365 patent, which

are reiterated and incorporated herein. Therefore, claim 56 of the '365 patent should be designated as corresponding to the count.

15. Claim 63

Claim 63 of the '365 patent is directed to:

> 63. Method for production of a modified DNA polymerase comprising steps of: providing a nucleic acid molecule encoding a thermostable DNA polymerase comprising the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q at its dNMP binding site wherein each N is independently any amino acid and mutagenizing said nucleic acid molecule to incorporate one or more base changes in the nucleotide base sequence to encode a tyrosine residue at position N_4 corresponding to T7 DNA polymerase residue 526 or at to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 6 and 20, for essentially the same reasons outlined above with respect to claims 1 and 55 of the '365 patent, which are reiterated and incorporated herein. Therefore, claim 63 of the '365 patent should be designated as corresponding to the count.

16. Claim 69

Claim 69 of the '365 patent is directed to:

> 69. Purified nucleic acid encoding a DNA polymerase according to claim 64.

Claim 64 of the '365 patent is directed to:

> 64. A purified Pol I-type DNA polymerase having a tyrosine residue at an amino acid position corresponding to T7

> DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site, whereby ability to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide is increased 20-fold compared to ability of a corresponding naturally occurring unmodified DNA polymerase.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 1 and 15. For essentially the same reasons outlined above with respect to claim 1 of the '365 patent, which are reiterated and incorporated herein, claim 69 of the '365 patent should be designated as corresponding to the count.

17. Claim 70

> 70. A method for production of a modified DNA polymerase having an increased ability to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to ability of a corresponding naturally occurring unmodified DNA polymerase which comprises the steps of modifying a nucleic acid molecule encoding a DNA polymerase to incorporate one or more base changes in its nucleotide base sequence to encode a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

This claim is therefore directed to the same patentable invention as the count and as Applicant's claims 6 and 20, for essentially the same reasons outlined above with respect to claim 1 of the '365 patent, which are reiterated and incorporated herein. Therefore claim 70 of the '365 patent should be designated as corresponding to the count.

C. Identification of Claims in Present Application Corresponding to the Proposed Count

Claims 1-6 and 15-20 are pending in the '421 application. In accordance with 37 C.F.R. § 41.202(a)(2), Applicant respectfully submits that each of these pending claims corresponds to the proposed count.

The proposed count, directed to a DNA molecule, is identical to claim 1 of the captioned application. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claim 2 of this application is dependent on claim 1 and relates to a DNA molecule of claim 1 further comprising a promoter. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claim 3 of this application is dependent on claim 2 and relates to a DNA molecule of claim 2, wherein the coding sequence is heterologous to the promoter. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claim 4 of this application relates to a host cell comprising the DNA molecule of claim 1. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claim 5 of this application is dependent on claim 4, and further defines the host cell to be *E. coli*. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claim 6 relates to a method of producing a mutant DNA polymerase by culturing a host cell comprising the DNA molecule of claim 2. This claim defines the same patentable invention as the count and should be designated as corresponding to the count.

Claims 15-20 relate to a DNA molecule comprising a coding sequence for a mutant *Taq* DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type *Taq* polymerase, a host cell comprising this DNA molecule, a method for producing a mutant DNA polymerase using this DNA molecule, and the mutant *Taq* DNA polymerase. Position 667 of *Taq* polymerase corresponds to position 570 of T5 polymerase (*see* Specification of the '421 application, at 8.) These claims define the same patentable invention as the count and should be designated as corresponding to the count.

Consequently, Applicant submits that claims 1-6 and 15-20, which are all the claims that are pending in the present application, should be designated as corresponding to the count.

III. Claim Chart Comparing the Claims of Each Party and Why the Claims Interfere

In accordance with 37 C.F.R. § 41.202(a)(3), the following claim chart compares claims 1-3, 5-11, 32, 40, 55, 56, 63, 69 and 70 of the '365 patent to the corresponding claims of the '421 application, and shows why an interference between these claims is proper:

The '365 Patent Claims	**The '421 Application Claims**	**Justification for Interference**
1. Modified gene encoding a modified Pol I-type DNA polymerase. . .	1. A DNA molecule comprising a coding sequence for a mutant protein, wherein said mutant protein is a mutant DNA polymerase selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase . . .	Claim 1 of the '365 patent refers to Pol I type DNA polymerases which encompasses at least *Streptococcus pneumoniae* polymerase I, *Thermus aquaticus* polymerase I, *Thermus flavus* polymerase I, T5 DNA polymerase I, and bacteriophage SP01 polymerase, which are specifically recited in claim 1 of the '421 application.
wherein said modified gene is modified to encode a tyrosine	wherein said mutant DNA polymerase comprises a	The specific substitution of Tyr for Phe at a

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site. . .	substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase.	position corresponding to Phe_{570} of wild-type T5 polymerase recited in claim 1 of the '421 application corresponds to a tyrosine substitution at position 762 of E. Coli and to a tyrosine substitution at position 526 of T7 DNA polymerase as recited in claim 1 of the '365 patent.
to increase ability of said modified DNA polymerase to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to the ability of a corresponding naturally-occurring unmodified DNA polymerase by at least 20-fold.		
See Claim 1, *supra.*	15. A DNA molecule as claimed in claim 1, wherein said mutant protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase.	In addition to the reasons put forth for claim 1 of the '365 patent *supra*, which are incorporated and reiterated herein, the substitution of tyrosine for phenylalanine at position 667 in Taq polymerase as recited in claim 15 of the '421 application corresponds to a tyrosine substitution at position 762 of E. coli Pol I and to a tyrosine substitution at 526 of T7 DNA polymerase as recited in claim 1 of the '365 patent.

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
2. The modified gene of claim 1 wherein said modified DNA polymerase has sufficient DNA polymerase activity for use in DNA sequencing when combined with any factor necessary for said DNA polymerase activity.	*See* Claim 1, *supra.*	A number of the enzymes recited in the Markush group of claim 1 of the '421 application have "sufficient DNA polymerase activity for use in DNA sequencing when combined with any factor necessary for said DNA polymerase activity" as recited by claim 2 of the '321 patent. Moreover, the specification of the '421 application provides that "[t]he mutant-DNA polymerases of this invention may also be used for DNA sequencing. . . ." Thus, the polymerases recited in claim 1 of the '421 application must have sufficient DNA polymerase activity for use in DNA sequencing as recited by claim 1 of the '365 patent.
3. The modified gene of claim 1 wherein said modified DNA polymerase has less than 500 units exonuclease activity per mg polymerase.	*See* Claim 1, *supra.*	A number of the enzymes recited in the Markush group of claim 1 of the '421 application have "less than 500 units exonuclease activity per mg polymerase" as recited by claim 2 of the '321 patent.

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		Moreover, the specification of the '421 application provides that "[m]ost preferably, the exonuclease activity is less than about 0.0001 units/mg protein." Thus, the polymerases recited in claim 1 of the '421 application have less than 500 units exonuclease activity per mg polymerase as recited by claim 1 of the '365 patent.
5. The modified gene of claim 1 wherein said modified DNA polymerase is a thermostable enzyme.	*See* Claim 1, *supra.*	A number of the enzymes recited in the Markush group of Claim 1 of the '421 application are thermostable enzymes as recited by claim 5 of the '365 patent.
6. The modified gene of claim 5 wherein said thermostable enzyme is selected from the group consisting of DNA polymerase encoded by *Thermus aquaticus*, *Thermus thermophilis*, *Thermus flavus*, and *Bacillus sterothermophilus*.	*See* Claim 1, *supra.*	A number of the enzymes recited in the Markush group of Claim 1 of the '421 application are recited in claim 6 of the '365 patent.
7. The modified gene of claim 1 wherein said ability of said polymerase to incorporate a dideoxynucleotide relative to	*See* Claim 1, *supra.*	The '365 patent defines the production of a non-discriminatory mutant *E. coli* DNA polymerase I as

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
the corresponding deoxynucleotide is increased at least 25-fold compared to the corresponding naturally-occurring unmodified DNA polymerase.		producing a DNA polymerase with an increase of at least 1000-fold in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase. The specification of the '421 application provides that "T5, Taq, Tne, Tma and other DNA polymerases can be made nondiscriminatory towards dideoxynucleotide and perhaps other nonnatural nucleotides by simple modification of a specific phenylalanine residue to a tyrosine residue." Thus, at least a subset of the nondiscriminatory DNA polymerases described and claimed in the '421 application, when defined as in the '365 patent, are at least 25-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		DNA polymerase.
8. The modified gene of claim 1 wherein said ability is increased at least 50-fold.	*See* Claim 1, *supra.*	For at least the same reasons as put forth for claim 7 of the '365 patent, which are incorporated and reiterated herein, at least a subset of the nondiscriminatory DNA polymerases described and claimed in the '421 application, when defined as in the '365 patent, are at least 50-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase.
9. The modified gene of claim 1 wherein said ability is increased at least 100-fold.	*See* Claim 1, *supra.*	For at least the same reasons as put forth for claim 7 of the '365 patent, which are incorporated and reiterated herein, at least a subset of the nondiscriminatory DNA polymerases described and claimed in the '421 application, when defined as in the '365 patent, are at least 100-fold increased in the ability to incorporate a dideoxynucleotide

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase.
10. The modified gene of claim 1 wherein said ability is increased at least 500-fold.	*See* Claim 1, *supra.*	For at least the same reasons as put forth for claim 7 of the '365 patent, which are incorporated and reiterated herein, at least a subset of the nondiscriminatory DNA polymerases described and claimed in the '421 application, when defined as in the '365 patent, are at least 500-fold increased in the ability to incorporate a dideoxynucleotide relative to the corresponding deoxynucleotide, compared to the corresponding naturally occurring unmodified DNA polymerase.
11. Method for production of a modified Pol I-type DNA polymerase having an increased ability to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to ability of a corresponding naturally-	6. A method for producing a protein, wherein said protein is a mutant DNA polymerase selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I,	For the same reasons put forth for claims 1 of the '365 patent, which are reiterated and incorporated herein, claim 11 of the '365 patent and claims 6 and 20 of the '421 application

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
occurring unmodified DNA polymerase comprising steps of:	*Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase,	encompass similar subject matter.
	comprising a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase,	
providing a nucleic acid molecule encoding a DNA polymerase and mutagenizing said nucleic acid molecule to incorporate one or more base changes in nucleotide base sequence at a region that encodes its dNMP binding site to encode a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in the dNMP binding site. . .	said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 2, and (b) isolating said protein from said host cell.	
to alter ability of said polymerase encoded by said nucleic acid to incorporate a		

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
dideoxynucleotide by at least 20-fold.		
See Claim 11, *supra.*	20. A method for producing a protein, . . .	*See* claim 11 of the '365 patent and claim 6 of the '421 application, *supra.*
	wherein said protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase, . . .	
	said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 16, and (b) isolating said protein from said host cell.	
32. Recombinant nucleic acid encoding any of the DNA polymerases of claims 27 to 31.	*See* Claim 1, *supra.*	Claim 32 of the '365 patent encompasses a recombinant nucleic acid molecule encoding: (a) a Taq DNA polymerase having a tyrosine residue substituted in place of the phenylalanine residue at position 667 in the wild-type Taq sequence; and (b) an *E. coli* Pol I DNA polymerase having a tyrosine residue

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		substituted in place of the phenylalanine residue at position 762 in the wild-type *E. coli* Pol I sequence. This claim therefore is directed to the same patentable invention as Applicant's claim 1, since "a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase" as recited in the proposed count would correspond to a substitution of tyrosine for phenylalanine at residue 667 of Taq, and at position 762 of *E. coli* Pol I.
40. Recombinant Nucleic acid encoding the polymerase of any of claims 33-39.	*See* Claim 1, *supra.*	Claim 40 of the '365 patent encompasses a recombinant nucleic acid molecule encoding: (a) a recombinant thermophilic DNA polymerase; (b) that discriminates against a ddNMP relative to a corresponding deoxynucleotide by less than a factor of 100;and (c) includes a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site. This claim is therefore directed to the same patentable invention as recited in Applicant's claim 1 and the proposed count, for essentially the same reasons outlined above with respect to claims 1, 7, and 32 of the '365 patent, which are reiterated and incorporated herein.
55. Purified nucleic acid encoding a DNA polymerase according to claim 47.	*See* Claim 1, *supra.*	Claim 55 of the '365 patent encompasses a purified nucleic acid encoding a non-naturally occurring thermostable DNA polymerase having a deoxynucleotide binding site with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q wherein each N_1-N_3 and N_5-N_7 is independently any amino acid and N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		Example 1 of the '421 application teaches the site-directed mutagenesis of a DNA molecule encoding T5 DNA polymerase to encode a mutant T5 DNA polymerase having an O-helix domain with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q where N_4 is a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526, and where each N_1-N_3 and N_5-N_7 is independently any amino acid. Because claim 1 of the '421 application encompass DNA molecules comprising a coding sequence for the mutant DNA polymerase of example 1 of the '421 application, claim 55 of the '365 patent is therefore directed to the same patentable invention as the proposed count and claim 1 of the '421 application.
56. Purified nucleic acid encoding a DNA polymerase according to claim 49.	*See* Claim 1, *supra.*	Claim 56 of the '365 patent encompasses a purified nucleic acid encoding a thermostable, non-naturally occurring modified *Thermus aquaticus* DNA polymerase having a

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
		deoxynucleotide binding site with the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N_7 Y G/Q with N_4 being a tyrosine residue at an amino acid position corresponding to 667 the naturally occurring unmodified polymerase. For essentially the same reasons outlined above with respect to claims 1 and 55 of the '365 patent, which are reiterated and incorporated herein. Claim 1 of the '421 application and claim 56 of the '365 patent should be designated as corresponding to the count.
63. Method for production of a modified DNA polymerase comprising steps of:	*See* Claims 6 and 20, *supra.*	For essentially the same reasons outlined above with respect to claims 1 and 55 of the '365 patent, which are reiterated and incorporated herein, claims 6 and 20 of the '421 application and claim 63 of the '365 patent should be designated as corresponding to the count.
providing a nucleic acid molecule encoding a thermostable DNA polymerase comprising the sequence K N_1 N_2 N_3 N_4 N_5 N_6 N7 Y G/Q at its dNMP binding site. . .		

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
wherein each N is independently any amino acid and mutagenizing said nucleic acid molecule to incorporate one or more base changes in the nucleotide base sequence to encode a tyrosine residue at position N_4 corresponding to T7 DNA polymerase residue 526 or at to *E. coli* DNA polymerase residue 762 in its dNMP binding site.		
69. Purified nucleic acid encoding a DNA polymerase according to claim 64.	*See* Claim 1, *supra.*	For essentially the same reasons outlined above with respect to claims 1of the '365 patent, which are reiterated and incorporated herein, claim 1 of the '421 application and claim 69 of the '365 patent should be designated as corresponding to the count.
70. A method for production of a modified DNA polymerase having an increased ability to incorporate a dideoxynucleotide relative to a corresponding deoxynucleotide compared to ability of a corresponding naturally occurring unmodified DNA polymerase. . .	*See* Claims 6 and 20, *supra.*	For essentially the same reasons outlined above with respect to claims 1 and 11 of the '365 patent, which are reiterated and incorporated herein, claims 6 and 20 of the '421 application and claim of the '365 patent should be designated as corresponding to the count.

The '365 Patent Claims	The '421 Application Claims	Justification for Interference
which comprises the steps of modifying a nucleic acid molecule encoding a DNA polymerase to incorporate one or more base changes in its nucleotide base sequence to encode a tyrosine residue at an amino acid position corresponding to T7 DNA polymerase residue 526 or at an amino acid position corresponding to *E. coli* DNA polymerase residue 762 in its dNMP binding site.		

IV. Explanation of Why Applicant Will Prevail on Priority

In accordance with 37 C.F.R. § 41.202(a)(4), Applicant respectfully asserts that the '421 application will prevail on priority against the '365 patent. In support of this assertion, Applicant refers to the remarks contained in the Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on December 4, 2001, and in the Supplemental Showing Under 37 C.F.R. §1.608(b) (and in the attachments thereto) filed on February 2, 2002, which are reiterated and incorporated herein by reference, to establish that Applicant reduced to practice his invention prior to the earliest available filing date of the '365 patent. Hence, Applicant respectfully submits that he will prevail in a contest of priority between the '421 application and the '365 patent.

V. Application of Claims 1-6 and 15-20 to the Disclosure of the '421 application

In accordance with 37 C.F.R. § 41.202(a)(5), the terms of claims 1-6 and 15-20 of the present application, identified above as corresponding to the count, are supported in the specification of the '421 application at least as shown in the following chart:

'421 Application Claims	**'421 Application Disclosure**
1. A DNA molecule comprising a coding sequence for a mutant protein, wherein said mutant protein is a mutant DNA polymerase . . .	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention . . ." Page 4, lines 4-5
selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase . . .	". . .it is also possible to prepare the following mutant DNA polymerases: Enzyme or source — Mutation Position *E. coli* DNA polymerase I — 762 *Streptococcus pneumoniae* — 711 *Thermus aquaticus* — 667 *Thermus flavus* — 666 *Thermus thermophilus* — 669 *Deinococcus radiodurans* — 747 *Bacillus caldotenax* — 711 *E. coli* bacteriophage T5 — 570 mycobacteriophage L5 — 438 *E. coli* bacteriophage SP01 — 692 *E. coli* bacteriophage SP02 — 447 *Thermatoga neapolitana* — 67 [] *Thermatoga maritima* — 730" Page 8, lines 15-30.
wherein said mutant DNA polymerase comprises a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase.	"The change in amino acid at the mutation positions above is from phenylalanine to tyrosine . . ." Page 8, lines 31-32.
[redacted]	[redacted]

'421 Application Claims	'421 Application Disclosure
2. The DNA molecule of claim 1, further comprising a promoter, . . .	"the recombinant DNA molecule encodes the protein, and also includes a promoter. . ." Page 15, lines 7-8.
wherein said promoter is in a position and orientation with respect to the coding sequence such that the mutant protein may be expressed in a cell under the control of said promoter.	"(The promoter and the structural gene are in such position and orientation with respect to each other that the promoter may regulate the expression of the gene in the cell)." Page 15, lines 9-11.
3. The molecule of claim 2, wherein said coding sequence is heterologous to said promoter.	"The promoter may be heterologous to the structural gene and may be inducible, e.g. a *lambda* P_L promoter, a *tac* promoter, or a *lac* promoter. Preferably, the structural gene is under control of a heterologous promoter." Page 15, lines 15-17.
4. A host cell comprising the DNA molecule of claim 1.	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention as well as host cells comprising the DNA molecule." Page 4, lines 4-6.
5. The host cell of claim 4, wherein said host cell is *E. coli*.	"Preferably, the mutant DNA polymerase gene is expressed and maintained in an *E. coli* host cell." Page 15, lines 13-14.

'421 Application Claims	'421 Application Disclosure
6. A method for producing a protein, wherein said protein is a mutant DNA polymerase . . .	"The invention also relates to a method for producing a protein, wherein said protein has a mutant DNA polymerase activity . . ." Page 4, lines 7-8.
selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase, . . .	". . .it is also possible to prepare the following mutant DNA polymerases: Enzyme or source — Mutation Position *E. coli* DNA polymerase I — 762 *Streptococcus pneumoniae* — 711 *Thermus aquaticus* — 667 *Thermus flavus* — 666 *Thermus thermophilus* — 669 *Deinococcus radiodurans* — 747 *Bacillus caldotenax* — 711 *E. coli* bacteriophage T5 — 570 mycobacteriophage L5 — 438 *E. coli* bacteriophage SP01 — 692 *E. coli* bacteriophage SP02 — 447 *Thermatoga neapolitana* — 67 [] *Thermatoga maritima* — 730" Page 8, lines 15-30.
comprising a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase, . . .	"The change in amino acid at the mutation positions above is from phenylalanine to tyrosine . . ." Page 8, lines 31-32.
said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 2, and (b) isolating said protein from said host cell.	"said method comprising the steps of: (i) culturing a host cell containing the DNA molecule of the invention, and (ii) isolating said protein from said host cell." Page 4, lines 9-13.

'421 Application Claims	'421 Application Disclosure
15. A DNA molecule as claimed in claim 1, wherein said mutant protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase.	"Examples of such mutant DNA polymerase proteins include . . . mutant Taq DNA polymerase, wherein Tyr^{667} is substituted for Phe^{667} of native Taq DNA polymerase;" Page 4, lines 14 and 16-17.
16. The DNA molecule of claim 15, further comprising a promoter, . . .	"the recombinant DNA molecule encodes the protein, and also includes a promoter. . ." Page 15, lines 7-8.
wherein said promoter is in a position and orientation with respect to the coding sequence such that the mutant protein may be expressed in a cell under the control of said promoter.	"(The promoter and the structural gene are in such position and orientation with respect to each other that the promoter may regulate the expression of the gene in the cell)." Page 15, lines 9-11.
17. The molecule of claim 16, wherein said coding sequence is heterologous to the promoter.	"The promoter may be heterologous to the structural gene and may be inducible, e.g. a *lambda* P_L promoter, a *tac* promoter, or a *lac* promoter. Preferably, the structural gene is under control of a heterologous promoter." Page 15, lines 15-17.
18. A host cell comprising the DNA molecule of claim 15.	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention as well as host cells comprising the DNA molecule." Page 4, lines 4-6.

'421 Application Claims	'421 Application Disclosure
19. The host cell of claim 18, wherein said host cell is *E. coli*.	"Preferably, the mutant DNA polymerase gene is expressed and maintained in an *E. coli* host cell." Page 15, lines 13-14.
20. A method for producing a protein, . . .	"The invention also relates to a method for producing a protein, wherein said protein has a mutant DNA polymerase activity . . ." Page 4, lines 7-8.
wherein said protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase, . . .	"Examples of such mutant DNA polymerase proteins include . . . mutant Taq DNA polymerase, wherein Tyr^{667} is substituted for Phe^{667} of native Taq DNA polymerase;" Page 4, lines 14 and 16-17.
said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 16, and (b) isolating said protein from said host cell.	"said method comprising the steps of: (i) culturing a host cell containing the DNA molecule of the invention, and (ii) isolating said protein from said host cell." Page 4, lines 9-13.

VI. Application of Claims 1-6 and 15-20 to the Disclosure of the Earlier Applications from which the '421 Application Claims Priority

The '421 application is a continuation of U.S. Application No. 08/576,759, filed December 21, 1995, which is a continuation of U.S. Application No. 08/537,397, filed October 2, 1995, which is a continuation-in-part of U.S. Application No. 08/525,057, filed September 8, 1995. Applicant respectfully submits that each of these priority applications represents a constructive reduction to practice of the subject matter of the claims in the '421 application that should be designated as corresponding to the count.

Therefore, upon declaration of an interference between the '421 application and the '365 patent, Applicant respectfully requests that he be accorded the benefit of the filing date of each of these priority applications.

In accordance with 37 C.F.R. § 41.202(a)(6), Applicant asserts that the terms of claims 1-6 and 15-20 of the '421 application, identified above as corresponding to the count, are supported in these earlier priority applications at least as shown in the following chart:

'421 Application Claims	**Disclosure in Priority Applications**
1. A DNA molecule comprising a coding sequence for a mutant protein, wherein said mutant protein is a mutant DNA polymerase . . .	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention . . ." Page 3, lines 14-15 of U.S. Appl. No. 08/525,057 Page 3, lines 25-26 of U.S. Appl. No. 08/537,397 Page 4, lines 4-5 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase . . .	". . .it is also possible to prepare the following mutant DNA polymerases: Enzyme or source — Mutation Position *E. coli* DNA polymerase I — 762 *Streptococcus pneumoniae* — 711 *Thermus aquaticus* — 667 *Thermus flavus* — 666 *Thermus thermophilus* — 669 *Deinococcus radiodurans* — 747 *Bacillus caldotenax* — 711 *E. coli* bacteriophage T5 — 570 mycobacteriophage L5 — 438 *E. coli* bacteriophage SP01 — 692 *E. coli* bacteriophage SP02 — 447 *Thermatoga neapolitana* — 67 [] *Thermatoga maritima* — 730" Page 6, lines 3-16 of U.S. Appl. No. 08/525,057 Page 8, lines 10-25 of U.S. Appl. No. 08/537,397 Page 8, lines 15-30 of U.S. Appl. No. 08/576,759
wherein said mutant DNA polymerase comprises a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase.	"The change in amino acid at the mutation positions above is from phenylalanine to tyrosine . . ." Page 6, lines 17-18 of U.S. Appl. No.08/525,057 Page 8, lines 26-27 of U.S. Appl. No. 08/537,397 Page 8, lines 31-32 of U.S. Appl. No. 08/576,759
[redacted]	[redacted]
2. The DNA molecule of claim 1, further comprising a promoter, . . .	"the recombinant DNA molecule encodes the protein, and also includes a promoter. . ." Page 11, lines 18-19 of U.S. Appl. No. 08/525,057 Page 15, lines 5-6 of U.S. Appl. No. 08/537,397 Page 15, lines 7-8 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
wherein said promoter is in a position and orientation with respect to the coding sequence such that the mutant protein may be expressed in a cell under the control of said promoter.	"(The promoter and the structural gene are in such position and orientation with respect to each other that the promoter may regulate the expression of the gene in the cell)." Page 11, lines 20-22 of U.S. Appl. No. 08/525,057 Page 15, lines 7-9 of U.S. Appl. No. 08/537,397 Page 15, lines 9-11 of U.S. Appl. No. 08/576,759
3. The molecule of claim 2, wherein said coding sequence is heterologous to said promoter.	"The promoter may be heterologous to the structural gene and may be inducible, e.g. a *lambda* P_L promoter, a *tac* promoter, or a *lac* promoter. Preferably, the structural gene is under control of a heterologous promoter." Page 11, lines 26-28 of U.S. Appl. No. 08/525,057 Page 15, lines 13-15 of U.S. Appl. No. 08/537,397 Page 15, lines 15-17 of U.S. Appl. No. 08/576,759
4. A host cell comprising the DNA molecule of claim 1.	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention as well as host cells comprising the DNA molecule." Page 3, lines 14-16 of U.S. Appl. No. 08/525,057 Page 3, lines 25-27 of U.S. Appl. No. 08/537,397 Page 4, lines 4-6 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
5. The host cell of claim 4, wherein said host cell is *E. coli.*	"Preferably, the mutant DNA polymerase gene is expressed and maintained in an *E. coli* host cell." Page 11, lines 24-26 of U.S. Appl. No. 08/525,057 Page 15, lines 11-12 of U.S. Appl. No. 08/537,397 Page 15, lines 13-14 of U.S. Appl. No. 08/576,759
6. A method for producing a protein, wherein said protein is a mutant DNA polymerase . . .	"The invention also relates to a method for producing a protein, wherein said protein has a mutant DNA polymerase activity . . ." Page 3, lines 17-18 of U.S. Appl. No. 08/525,057 Page 4, lines 1-2 of U.S. Appl. No. 08/537,397 Page 4, lines 7-8 of U.S. Appl. No. 08/576,759
selected from the group consisting of: *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase I, *Streptococcus pneumoniae* polymerase, *Thermus aquaticus* polymerase, *Thermus flavus* polymerase, *Thermus thermophilus* polymerase, *Deinococcus radiodurans* polymerase, *Bacillus caldotenax* polymerase, *E. coli* bacteriophage T5 polymerase, mycobacteriophage L5 polymerase, *Thermatoga maritima* polymerase, and *E. coli* bacteriophage SP01 polymerase, . . .	". . .it is also possible to prepare the following mutant DNA polymerases: Enzyme or source — Mutation Position *E. coli* DNA polymerase I 762 *Streptococcus pneumoniae* 711 *Thermus aquaticus* 667 *Thermus flavus* 666 *Thermus thermophilus* 669 *Deinococcus radiodurans* 747 *Bacillus caldotenax* 711 *E. coli* bacteriophage T5 570 mycobacteriophage L5 438 *E. coli* bacteriophage SP01 692 *E. coli* bacteriophage SP02 447 *Thermatoga neapolitana* 67 [] *Thermatoga maritima* 730" Page 6, lines 3-16 of U.S. Appl. No. 08/525,057 Page 8, lines 10-25 of U.S. Appl. No. 08/537,397 Page 8, lines 15-30 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
comprising a substitution of Tyr for Phe at a position in said polymerase corresponding to Phe_{570} of wild-type T5 polymerase, . . .	"The change in amino acid at the mutation positions above is from phenylalanine to tyrosine . . ." Page 6, lines 17-18 of U.S. Appl. No. 08/525,057 Page 8, lines 26-27 of U.S. Appl. No. 08/537,397 Page 8, lines 31-32 of U.S. Appl. No. 08/576,759
said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 2, and (b) isolating said protein from said host cell.	"said method comprising the steps of: (i) culturing a host cell containing the DNA molecule of the invention, and (ii) isolating said protein from said host cell." Page 3, lines 19-23 of U.S. Appl. No. 08/525,057 Page 4, lines 3-7 of U.S. Appl. No. 08/537,397 Page 4, lines 9-13 of U.S. Appl. No. 08/576,759
[redacted]	[redacted]
15. A DNA molecule as claimed in claim 1, wherein said mutant protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase.	"Examples of such mutant DNA polymerase proteins include . . . mutant Taq DNA polymerase, wherein Tyr^{667} is substituted for Phe^{667} of native Taq DNA polymerase;" Page 3, lines 24 and 26-27 of U.S. Appl. No. 08/525,057 Page 4, lines 8 and 10-11 of U.S. Appl. No. 08/537,397 Page 4, lines 14 and 16-17 of U.S. Appl. No. 08/576,759
[redacted]	[redacted]
16. The DNA molecule of claim 15, further comprising a promoter, . . .	"the recombinant DNA molecule encodes the protein, and also includes a promoter. . ." Page 11, lines 18-19 of U.S. Appl. No. 08/525,057 Page 15, lines 5-6 of U.S. Appl. No. 08/537,397 Page 15, lines 7-8 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
wherein said promoter is in a position and orientation with respect to the coding sequence such that the mutant protein may be expressed in a cell under the control of said promoter.	"(The promoter and the structural gene are in such position and orientation with respect to each other that the promoter may regulate the expression of the gene in the cell)." Page 11, lines 20-22 of U.S. Appl. No. 08/525,057 Page 15, lines 7-9 of U.S. Appl. No. 08/537,397 Page 15, lines 9-11 of U.S. Appl. No. 08/576,759
17. The molecule of claim 16, wherein said coding sequence is heterologous to the promoter.	"The promoter may be heterologous to the structural gene and may be inducible, e.g. a *lambda* P_L promoter, a *tac* promoter, or a *lac* promoter. Preferably, the structural gene is under control of a heterologous promoter." Page 11, lines 26-28 of U.S. Appl. No. 08/525,057 Page 15, lines 13-15 of U.S. Appl. No. 08/537,397 Page 15, lines 15-17 of U.S. Appl. No. 08/576,759
18. A host cell comprising the DNA molecule of claim 15.	"The invention also relates to a DNA molecule which codes for the mutant DNA polymerase of the present invention as well as host cells comprising the DNA molecule." Page 3, lines 14-16 of U.S. Appl. No. 08/525,057 Page 3, lines 25-27 of U.S. Appl. No. 08/537,397 Page 4, lines 4-6 of U.S. Appl. No. 08/576,759

'421 Application Claims	Disclosure in Priority Applications
19. The host cell of claim 18, wherein said host cell is *E. coli*.	"Preferably, the mutant DNA polymerase gene is expressed and maintained in an *E. coli* host cell." Page 11, lines 24-26 of U.S. Appl. No. 08/525,057 Page 15, lines 11-12 of U.S. Appl. No. 08/537,397 Page 15, lines 13-14 of U.S. Appl. No. 08/576,759
20. A method for producing a protein, . . .	"The invention also relates to a method for producing a protein, wherein said protein has a mutant DNA polymerase activity . . ." Page 3, lines 17-18 of U.S. Appl. No. 08/525,057 Page 4, lines 1-2 of U.S. Appl. No. 08/537,397 Page 4, lines 7-8 of U.S. Appl. No. 08/576,759
wherein said protein is a mutant Taq DNA polymerase comprising a substitution of Tyr for Phe_{667} of wild-type Taq polymerase, . . .	"Examples of such mutant DNA polymerase proteins include . . . mutant Taq DNA polymerase, wherein Tyr^{667} is substituted for Phe^{667} of native Taq DNA polymerase;" Page 3, lines 24 and 26-27 of U.S. Appl. No. 08/525,057 Page 4, lines 8 and 10-11 of U.S. Appl. No. 08/537,397 Page 4, lines 14 and 16-17 of U.S. Appl. No. 08/576,759
said method comprising: (a) culturing a host cell comprising the DNA molecule of claim 16, and (b) isolating said protein from said host cell.	"said method comprising the steps of: (i) culturing a host cell containing the DNA molecule of the invention, and (ii) isolating said protein from said host cell." Page 3, lines 19-23 of U.S. Appl. No. 08/525,057 Page 4, lines 3-7 of U.S. Appl. No. 08/537,397 Page 4, lines 9-13 of U.S. Appl. No. 08/576,759

VII. Requirement to Show Priority under 35 U.S.C. 102(g) in Compliance with 37 C.F.R. §41.202(d)

As noted above, the present application has an earliest possible effective filing date of September 8, 1995. Thus, the earliest constructive reduction to practice available to Applicant is later than the apparent earliest constructive reduction to practice for the '365 patent of either November 10, 1994 or October 17, 1994.[2] However, Applicant respectfully asserts that the '421 application has priority to the claimed invention under 35 U.S.C. § 102(g) over the '365 patent, based on an earlier actual reduction to practice. In support of this assertion, and to provide the required showing under 37 C.F.R. § 41.202(d), Applicant refers to the remarks contained in the Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on December 4, 2001, and in the Supplemental Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed February 2, 2002, which are reiterated and incorporated herein by reference. This showing clearly establishes that Applicant reduced his claimed invention to practice prior to the earliest available filing date of the '365 patent. Hence, Applicant will prevail in a contest of priority between the '421 application and the '365 patent.

VIII. Claims in the '365 Patent That Should Not be Designated as Corresponding to the Count

As requested by the Examiner, Applicant provides the following comments concerning the remaining claims in the '365 patent that Applicant contends should not be designated as corresponding to the proposed count.

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[2] This statement is not to be construed as an admission or concession by Applicant that the '365 patent actually has a constructive reduction to practice date of either November 10, 1994 or October 17, 1994. Applicant expressly reserves the right to establish that the disclosures of the applications from which the '365 patent claims priority are not enabling for, and/or do not provide adequate written description of, the claims of the '365 patent, as required by 35 U.S.C. § 112, ¶ 1.

A. Claims Relating to DNA Polymerase II Enzymes

Claims 83-85, 87-89, and 108 of the '365 patent are directed to subject matter related DNA polymerase II. These claims are not encompassed by the proposed count because the proposed count encompasses DNA polymerase I and not DNA polymerase II. Thus, claims 83-85, 87-89, and 108 of the '365 patent should not be designated as corresponding to the proposed count.

B. Claims Relating to DNA Polymerases

Claims 4, 27-31, 33-39, 42-43, 46-54, 64-68, 86, 105-107 of the '365 patent are directed to a DNA polymerase. These claims are not encompassed by the proposed count because the proposed count encompasses, *inter alia*, a DNA molecule comprising a coding sequence for a mutant protein and not a DNA polymerase. Thus, claims 4, 27-31, 33-39, 42-43, 46-54, 64-68, 86, 105-107 of the '365 patent should not be designated as corresponding to the proposed count.

C. Claims Relating to Methods of Use of a Modified DNA Polymerase

Claims 12-18, 20-26, 41, 44-45, 71-74, 82, 90-96, 98-104 of the '365 patent are directed to methods of use of modified DNA polymerases. These claims are not encompassed by the proposed count because the proposed count encompasses, *inter alia*, a DNA molecule comprising a coding sequence for a mutant protein and not methods of use of a DNA polymerase. Thus, claims 12-18, 20-26, 41, 44-45, 71-74, 82, 90-96, 98-104 of the '365 patent should not be designated as corresponding to the proposed count.

D. Claims Related to Kits Comprising a DNA Polymerase

Claims 19, 57-60, 75-81, and 97 of the '365 patent are directed to kits comprising a DNA polymerase. These claims are not encompassed by the proposed count because

the proposed count encompasses, *inter alia*, a DNA molecule comprising a coding sequence for a mutant protein and not a kit comprising a DNA polymerase. Thus, claims 19, 57-60, 75-81, and 97 of the '365 patent should not be designated as corresponding to the proposed count.

E. Claims Related to Solutions Comprising a DNA Polymerase

Claims 61 and 62 of the '365 patent are directed to solutions comprising a DNA polymerase. These claims are not encompassed by the proposed count because the proposed count encompasses, *inter alia*, a DNA molecule comprising a coding sequence for a mutant protein and not a solution comprising a DNA polymerase. Thus, claims 61 and 62 of the '365 patent should not be designated as corresponding to the proposed count.

IX. Other Matters

Applicant notes that a restriction requirement was issued in the '421 application on September 20, 2000. This restriction requirement restricted certain originally filed claims of the '421 application, encompassing the subject matter noted in Section VIII B-E above, into restriction groups that were separate from the subject matter presently claimed in the '421 application. As a result of the restriction requirement, Applicant cancelled the claims of the '421 application that encompassed the subject matter noted in Section VIII B-E above, without prejudice or disclaimer. Hence, the '421 application has no claims currently pending that are drawn to the subject matter of the claims in the '365 patent noted in Section VIII B-E above. However, Applicant expressly reserves the right to file one or more divisional or continuing applications directed to such subject matter,

and to suggest interference with at least the claims of the '365 patent listed above in Section VIII B-E.

X. Summary

In light of the foregoing, and remarks contained in Applicant's Request for Interference filed on December 4, 2001, and in the Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on December 4, 2001, and in the Supplemental Showing Under 37 C.F.R. § 1.608(b) (and the attachments thereto) filed on February 2, 2002, which are reiterated and incorporated herein by reference, Applicant respectfully suggests that an interference be expeditiously declared between the present application and U.S. Patent No. 5,614,365. Early notification to this effect is earnestly solicited.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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